Efficient Preparation of Polysubstituted Naphthyl Phenyl and Dinaphthyl Ketones from Naphthalenic Esters by Anionic Homo-Fries Rearrangement

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Abstract: The anionic homo-Fries rearrangement of naphthalenic esters can be effected in good yield to provide regiocontrolled access to complex diaryl ketones.

Key words: Homo-Fries rearrangement, naphthyl phenyl ketone, dinaphthyl ketone, xanthone

In the context of a program on the synthesis of the new topoisomerase I inhibitor hypoxyxylerone (Figure 1)[1,2] and derivatives,[3] the potential of the anionic homo-Fries rearrangement of naphthyl-phenyl and naphthyl-naphthyl esters for regioselective xanthone formation seemed worth investigating.

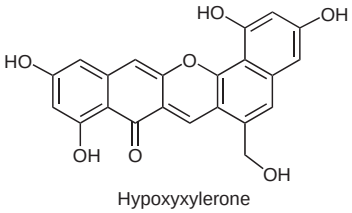
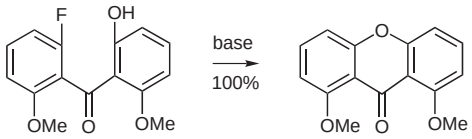


Figure 1

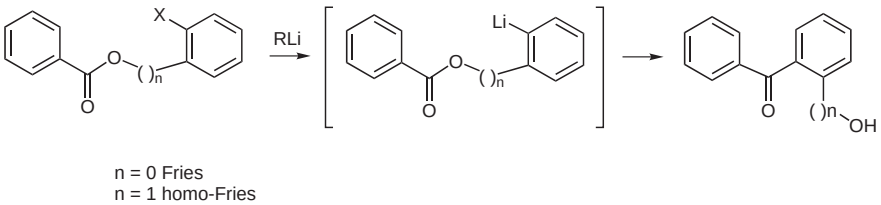
In its simplest form, the anionic Fries rearrangement involves halogen-metal exchange in an *ortho*-halophenyl benzoate, which is followed by intramolecular carbonyl attack by the carbanion to produce the corresponding benzophenone (Scheme 1, n = 0).[4] This rearrangement, which is usually more efficient when a methoxyl substituent is present *ortho* to the ester carbonyl,[5] has enjoyed use in synthesis due, in part, to the better yields that can usually be realized relative to the intermolecular variant and the possibility of easily and regioselectively transforming the products into xanthones (e.g., Scheme 2). The homo-Fries rearrangement,[4] which is distinguished from the Fries by an additional carbon in the halide portion of the ester (Scheme 1, n = 1), has also found synthetic application, most notably in balanol-related work.[6]



Scheme 2

In this paper we present the results of a study of the anionic homo-Fries rearrangement of naphthyl-phenyl and naphthyl-naphthyl esters, which has been found to afford effectively naphthyl phenyl and dinaphthyl ketones, key intermediates for the synthesis of variously substituted tetra- and pentacyclic xanthones.

The naphthyl-phenyl esters **1a**,**b**[7] on exposure to *n*-BuLi under carefully studied conditions suffered homo-Fries rearrangement to give the naphthyl phenyl ketones **2a**,**b** in ca. 50% yield (Scheme 3). THF in the absence of additives such as HMPA or 12-crown-4 proved to be the most suitable milieu for these reactions. The amount of *n*-BuLi was found to be critical, with the use of over 1.1 equivalents leading to butylated products. Ester concentration was also found to be an important parameter, the highest yields being achieved with a concentration of 0.25 M. At lower concentrations, the yields decreased; at 0.06 M there was little conversion. These results are consistent with the formation of an intermediate dimeric species, as proposed by Horne and Rodrigo.[5]



Scheme 1

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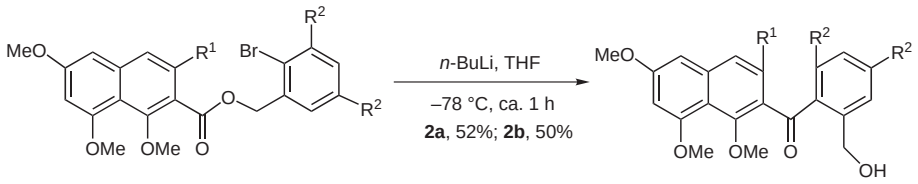

1a, R^1=OMe; R^2=OBn
1b, R^1=OBn; R^2=OMe

2a, R^1=OMe; R^2=OBn
2b, R^1=OBn; R^2=OMe

Scheme 3

That the naphthyl-phenyl anionic homo-Fries rearrangement is not particularly sensitive to the sense of the reaction was shown through treatment of ester **3a** (Scheme 4) with *n*-butyllithium, which produced naphthyl phenyl ketone **4a** in comparable yield (41%).

A dramatic increase in yield was observed, however, in the transformation of fluoride **3b** into ketone **4b** (85%), a result that can be understood on the basis of both steric and electronic effects.[5] Coupled with the clean, regioselective ring closure that is possible with an *ortho*-fluoro substituent (F vs OMe, Scheme 2), this type of anionic homo-Fries rearrangement should allow particularly efficient formation of complex, polycyclic xanthones.

The naphthyl-naphthyl esters **5a**,**b** were also examined under the above rearrangement conditions (Scheme 5). To our satisfaction, these first examples of naphthyl-naphthyl anionic homo-Fries rearrangements proceeded smoothly and highly reproducibly (300-mg scale), in spite of the relative complexity of the systems, to furnish the corresponding dinaphthyl ketones **6a**,**b**. Dinaphthyl ketone **6a**, obtained in 55% yield (65% brsm),[8] has been converted into a potential xanthone intermediate for the synthesis of hypoxyxlerone by methylation, debenzylation, and base-induced cyclization.[3]

In summary, we have demonstrated that the anionic homo-Fries rearrangement can be extended to different naphthyl-phenyl and naphthyl-naphthyl systems to produce in synthetically useful yields naphthyl phenyl and dinaphthyl ketones, key intermediates for the preparation of complex xanthones.[9]

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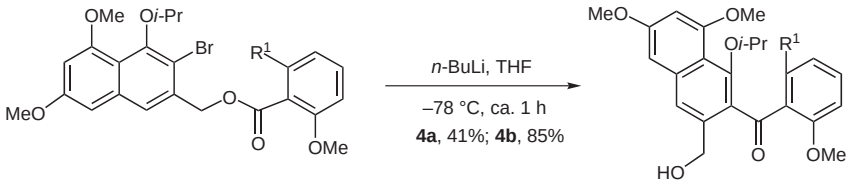
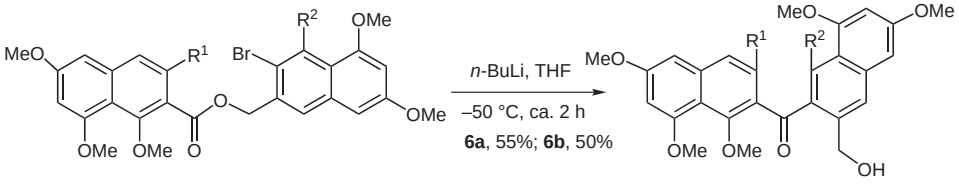


3a, R^1=OMe
3b, R^1=F

4a, R^1=OMe
4b, R^1=F

Scheme 4



5a, R^1=OBn; R^2=OMe
5b, R^1=OMe; R^2=O*i*-Pr

6a, R^1=OBn; R^2=OMe
6b, R^1=OMe; R^2=O*i*-Pr

Scheme 5

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(7) (a) Esters **1a**,**b**, **3a**,**b**, **5a**,**b** were prepared by coupling under Mitsunobu conditions. See: Mitsunobu, O. *Synthesis* **1981**, 1. (b) See also: Hughes, D. L. *Org. React.* **1992**, *42*, 335. (c) For the preparation of the naphthalenic precursors, see ref.[3]
(8) **Anionic Homo-Fries Reaction of Ester 5a:** A solution of ester **5a** (269 mg, 0.397 mmol) in THF (1.59 mL, from which residual water had been eliminated with *n*-BuLi and *o*-phenanthroline) under argon was cooled to –55 to –45 °C and treated dropwise with *n*-BuLi (0.203 mL, 0.437 mmol). After being stirred for 2 h at this temperature, the reaction mixture was treated with sat. aq NH_4Cl solution, allowed to warm to 20 °C, and diluted with EtOAc. The crude product was isolated with EtOAc in the usual manner and purified by radial thin-layer chromatography (hexane in EtOAc, 9:1 to 1:1) to give 43 mg (16%) of recovered starting material, 32 mg (13%) of debrominated starting material, and 130 mg (55%, 65% brsm) of dinaphthyl ketone **6a** as a white solid. Ketone **6a**: Mp 220–224 °C (cyclohexane–dichloromethane); IR(neat): 3454, 1619, 1573 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.41 (s, 3 H), 3.57 (s, 3 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 3.90 (s, 6 H), 4.55 (d, *J* = 6.8 Hz, 2 H), 5.03 (s, 2 H), 6.37 (d, *J* = 2.4 Hz, 1 H), 6.45 (d, *J* = 2.4 Hz, 1 H), 6.60 (d, *J* = 2.1 Hz, 1 H), 6.70 (d, *J* = 2.1 Hz, 1 H), 6.87 (s, 1 H), 7.05–7.35 (m, 5 H), 7.41 (s, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.3 (CH_3), 55.4 (CH_3), 56.0 (CH_3), 63.9 (CH_3), 64.0 (CH_3), 64.1 (CH_3), 64.7 (CH_2), 70.2 (CH_2), 97.4 (CH), 98.7 (CH), 99.3 (CH), 103.2 (CH), 111.1 (C), 114.7 (C), 124.4 (CH), 125.4 (C), 127.4 (2 CH), 127.8 (CH), 128.3 (2 CH), 131.3 (C), 136.3 (C), 139.3 (C), 139.5 (C), 155.1 (C), 156.0 (C), 157.6 (C), 157.8 (C), 159.4 (C), 159.6 (C), 198.6 (C); MS (DCI): *m/z* (%) = 599 (50) [MH^+], 279 (100); Anal. Calcd for $C_{35}H_{34}O_9$: Mr, 598.2203. Found: Mr (mass spectrum, EI), 598.2211.
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